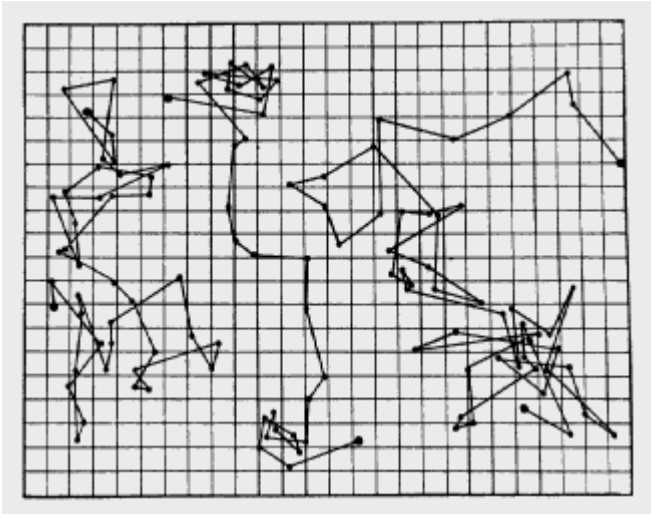
Lecture 10:
Brownian Motion, Random Walk & Diffusion
Side Chains of Amino Acids

Lecturer:
Prof. Brigita Urbanc (brigita@drexel.edu)

Stochastic Processes: Brownian Motion

- micron size Brownian particles, suspended in solution, move as a result of impact from solvent atoms

Perrin's plot



- stochastic variable: a sum of a large number of random steps

⇒

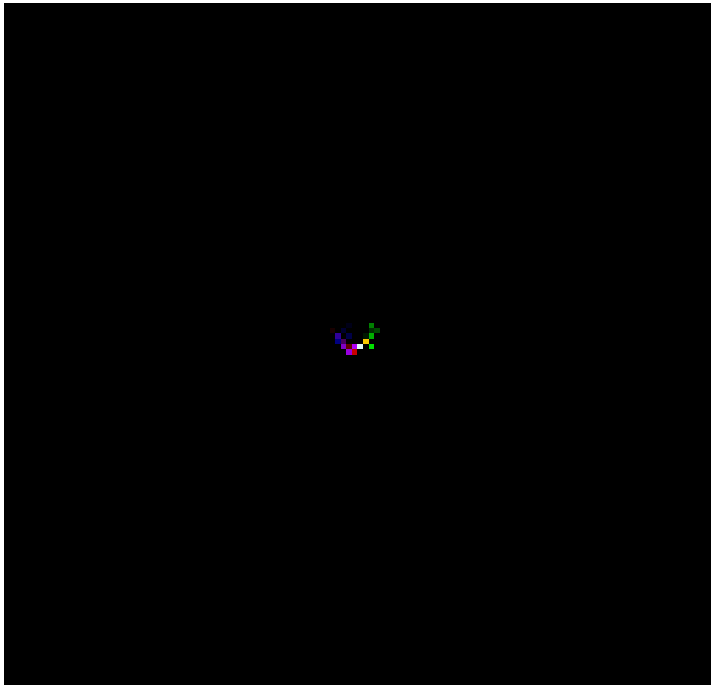
Brownian step

- stochastic processes need to be treated in a statistical manner
- Einstein's prediction in 1905 experimentally confirmed by Perrin in 1909

The Simplest Stochastic Process: Random Walk

⇔ random process consisting of a sequence of discrete steps of fixed length

- random walk in 1D



- W(k,n) – probability that After n steps, the particle will be k steps away from the starting point

- f – # of forward steps
- b – # of backward steps
- f+b=n & f-b=k ⇨ f=(n+k)/2 & b=(n-k)/2

- $W(k,n) = n!/ f! (n-f)! \, 2^{-n} = 2^{-n} \, n! / [(n+k)/2]! \, [(n-k)/2]!$

  # of ways to choose a forward step out of total n steps

- W(k,n) – BINOMIAL distribution

- for $n \gg k \gg 1 \Rightarrow$ Gaussian distribution in k

- Sterling's formula: $\ln n! \sim n \ln n - n + \ln (2\pi n)^{1/2}$

- expand to the lowest order in k/n

$$\downarrow$$

Gaussian distribution in k:

$$W(k,n) \approx (2/\pi n)^{1/2} \exp(-k^2/2n)$$

Diffusion

- translate the random walk Gaussian distribution into a physical situation: $k = x/x_0$ & $n = t/t_0$

- x_0 & t_0 – unit length & time step

  $\Rightarrow$ diffusion law in 1D – probability density

  $$W(x,t) = 1/(4\pi Dt)^{1/2} \exp(-x^2/4Dt)$$

  [3D: $W(r,t) = 1/(4\pi Dt)^{3/2} \exp(-r^2/4Dt)$]

- D – diffusion constant: $D = x_0^2/2t_0$
- normalization at t>0: $\int_{-\infty}^{\infty} dx\, W(x,t) = 1$
- normalization at $t \to 0$: $W(x,t) \to \delta(x)$
- $\langle x^2 \rangle = 2Dt$

Mean square displacement proportional to $t^{1/2}$!

Diffusion as a Random Walk (RW) Process

- one RW step – time to dissipate the molecules's kinetic energy (dissipation due to friction):

$$m\,dv/dt = F_{friction} = -3\pi(2R)\eta\,v \text{ (Stokes's law)}$$

$$\Downarrow$$

$$t_{kinetic} = m/[3\pi(2R)\eta] \text{ (2R – diameter of a mol.)}$$

- $t_{kinetic}$ – kinetic time, in which a molecule forgets the prior direction of motion – one step in a RW
- diffusion time $t_{diffusion}$:
  - in $t_{kinetic}$ a molecule moves by $\Delta l = v\,t_{kinetic}$ in a random direction: $l_{n+1} = l_n \pm \Delta l \Rightarrow l_{n+1}^2 = l_n^2 + \Delta l^2$
  - in any time t, the displacement $l_t^2 = (t/t_{kinetic})\,\Delta l^2$

→ **the final expression for the displacement:**

$$l_t^2 = t\,[k_B T/(\pi \eta R)]$$

characteristic time for diffusion is time needed to move by one molecular diameter 2R: $l_t = 2R$

$$\Downarrow$$

$$t_{diffusion} = 4\pi R^3 \eta/(k_B T)$$

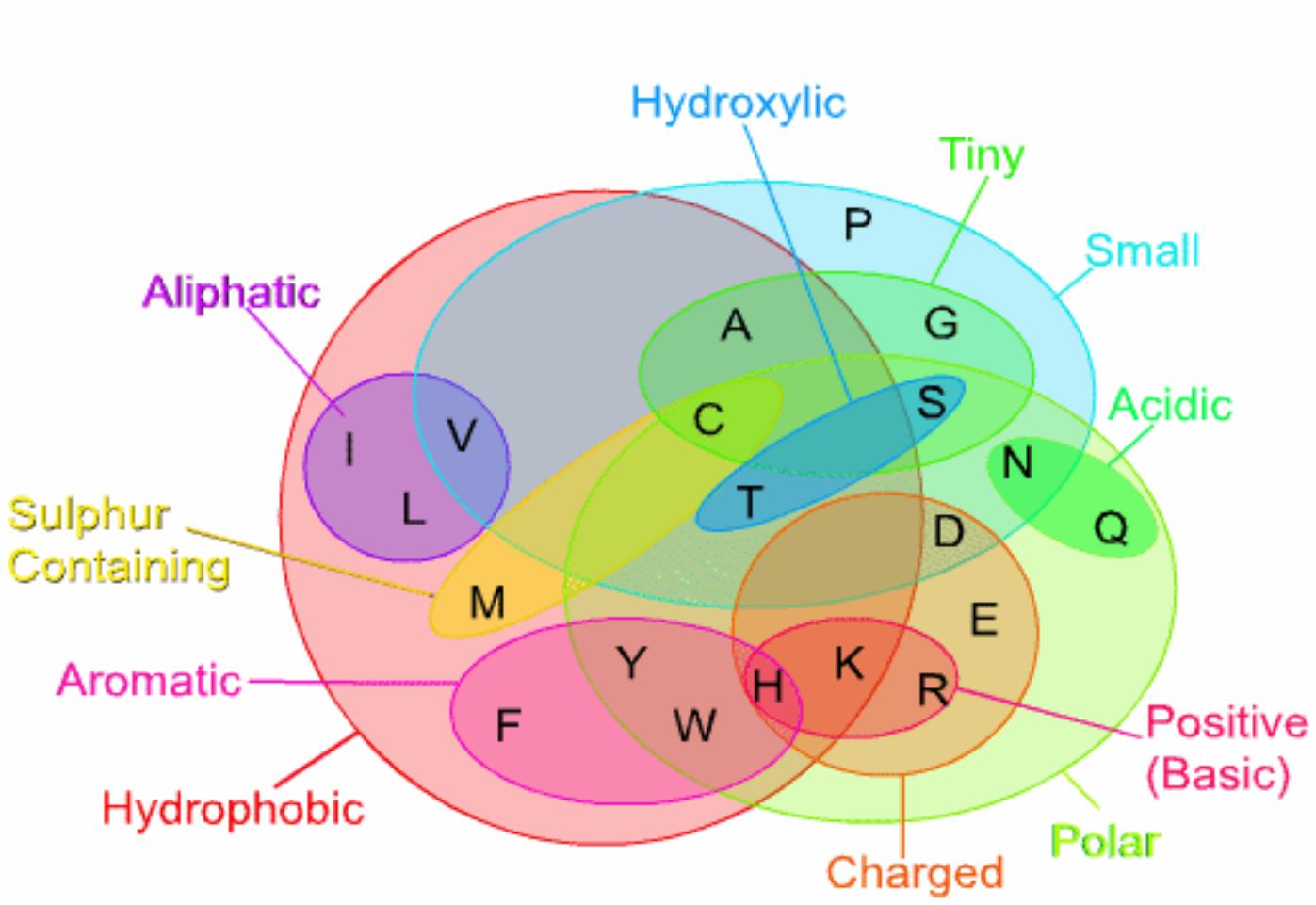
water viscosity $\eta = 0.01$ **g** cm^{-1} s^{-1} **&** $k_B T \sim 600$ **cal** mol^{-1}

$$\Downarrow$$

$$t_{diffusion} = 0.4 \times 10^{-9}\ s\ (2R/nm)^3$$

2R/nm – molecule's diameter in nanometers

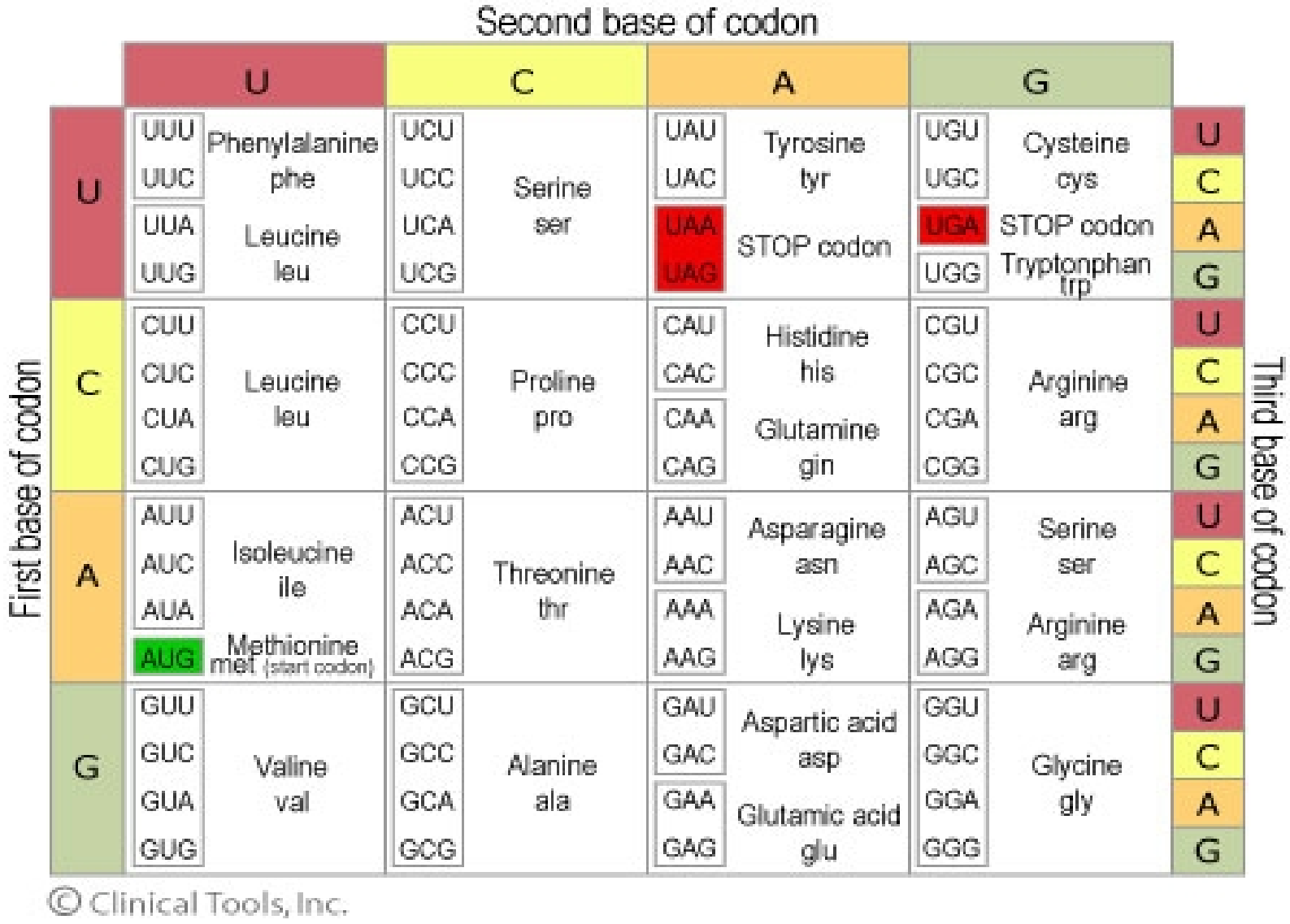
20 standard, DNA encoded amino acid residues



Amino Acids

A alanine (ala)
R arginine (arg)
N asparagine (asn)
D aspartic acid (asp)
C cysteine (cys)
Q glutamine (gln)
E glutamic acid (glu)
G glycine (gly)
H histidine (his)
I isoleucine (ile)
L leucine (leu)
K lysine (lys)
M metioneine (met)
F phenyalanine (phe)
P proline (pro)
S serine (ser)
T threonine (thr)
W trytophan (trp)
Y tyrosine (tyr)

DNA encoding of amino acids (redundancy)



Properties of individual amino acids:

- **Pro: "structure breaker":**
  - **only 1 HB (instead of 2)**
  - **found at the N-terminus of α-helix (N group "free" & Φ angle ~60° close to the α-helix requirements)**
- **Gly: prefers irregular structure (rather than α-helix or β-sheet) due to less restricted dihedral angles**
- **Ala: a more narrow range of (Φ, ψ) angles prefers the most α-helix but also β-sheet**
- **hydrophobic residues larger than Ala prefer β-sheet (allows for more room for their large side chains: C_γ atoms)**

- **amino acids with polar groups:**
  - **prefer irregular coil structure**
  - **surface (in contact with solvent) regions to form HBs with water molecules**
- **tryptophan (Trp) & tyrosine (Tyr) exceptions:**
  - **both with large hydrophobic parts**
  - **in addition small dipole**
- **Cysteine (Cys) also exception:**
  - **SH side-chain group can form *weak* HBs**
  - **two Cys participate in disulfide bonding**
- **Negatively charged residues prefer the N-terminus of and positively charged residue prefer the C-terminus of α-helices**

Basic principles of globular protein structure formation:

- **hydrophilic residues on protein surface (HBs with water)**
- **charged hydrophilic resist moving from high ε (water) to low ε (protein interior)**
- **hydrophobic residues comprise the hydrophobic core of globular proteins (hydrophobic effect proportional to the surface of hydrophobic side-chain groups)**
- **adhesion of hydrophobic groups: the main driving force of protein globule formation**
- **secondary structure (i.e. HBs) formed prior or during adhesion: α-helices and β-sheets possess hydrophobic & hydrophilic surfaces**

Role of pH in the charge state of individual amino acids

- pK_a values: $pK_a = - \log_{10} K_a$

  K_a – acid dissociation constant in equilibrium

  $K_a = [A^-][H^+]/[AH]$ with unit mol/l

  (quotient of ion concentrations)

- pH definition: $pH = - \log_{10}[H^+]$
- pH increase → decrease in the conc. of H^+ ions $[H^+]$
  - neutral group acquires negative charge
  - positively charged group gets discharged
  - the width of the transition is 2 units of pH

  (ratio of charged:uncharged from 10:1 to 1:10)

$$pK_a = -\log_{10} K_a = -\log_{10}\{[A^-][H^+]/[AH]\}$$
$$= -\log_{10}[A^-] - \log_{10}[H^+] + \log_{10}[AH]$$
$$= pH - \log_{10}[A^-] + \log_{10}[AH]$$

$$pK_a - pH = \log_{10}[AH]/[A^-] \rightarrow 10^{pKa - pH} = [AH]/[A^-]$$

$$W_0 = \{1 + 10^{pKa - pH}\}^{-1} = [A^-]/\{[AH] + [A^-]\}$$

– probability of uncharged state for a positively charged group (note: at $pK_a = pH$, $W_0 = ½$): Arg, Lys, His

$$W_0 = \{1 + 10^{-(pKa - pH)}\}^{-1} = [AH]/\{[AH] + [A^-]\}$$

– probability of uncharged state for a negatively charged group (note: at $pK_a = pH$, $W_0 = ½$): Asp, Glu

For a positively charged group, the free energy of uncharging:

$$F_0 = -k_B T \ln W_0 \approx 0 \text{ (for pH} > \text{pK}_a\text{)}$$

$$\approx 2.3\, k_B T\, (\text{pK}_a - \text{pH}) > 0 \text{ at pH} < \text{pK}_a$$

For a negatively charged group, the free energy of uncharging:

$$F_0 = -k_B T \ln W_0 \approx 0 \text{ (for pH} < \text{pK}_a\text{)}$$

$$\approx -2.3\, k_B T\, (\text{pK}_a - \text{pH}) > 0 \text{ at pH} > \text{pK}_a$$

In both cases, it costs free energy to discharge, but the overall amount of free energy is only ~ several units of $k_B T$.

pK_a values of individual amino acids:

Asp(D) 3.9 – charged at neutral pH
Glu(E) 4.3 – charged at neutral pH
Arg(R) 12.0 – charged at neutral pH
Lys(K) 10.5 – charged at neutral pH
His(H) 6.08 – only partially charged at neutral pH
Cys(C) 8.28 – uncharged at neutral pH
Tyr(Y) 10.1 – uncharged at neutral pH